

What is claimed is:

1. A modified IgG comprising an IgG constant domain comprising one or more amino acid modifications relative to a wild-type IgG constant domain, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type IgG constant domain, and wherein the one or more amino acid modifications are at one or more of positions 251, 253, 255, 285-290, 308-314, 385-389, and 428-435.
2. A modified non-human IgG comprising a non-human IgG constant domain comprising one or more amino acid modifications relative to a wild-type non-human IgG constant domain, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type non-human IgG constant domain, and wherein the one or more amino acid modifications are at one or more of positions 251-256, 285-290, 308-314, 385-389, and 428-436, with the proviso that the one or more amino acid modifications do not include substitution with leucine at position 252, serine at position 254, and phenylalanine at position 256.
3. A modified human or humanized IgG comprising a human IgG constant domain comprising one or more amino acid modifications relative to a wild-type human IgG constant domain, wherein the modified human or humanized IgG has an increased half-life compared to the half-life of a human or humanized IgG having the wild-type human IgG constant domain, and wherein the one or more amino acid modifications are at one or more of positions 251-256, 285-290, 308-314, 385-389, and 428-436.
4. The modified IgG according to claim 1, 2, or 3, wherein at least one of the amino acid modifications is an amino acid substitution.
5. The modified IgG according to claim 1, 2, or 3, wherein at least one of the amino acid modifications is an amino acid deletion.
6. The modified IgG according to claim 1, 2, or 3, wherein at least one of the amino acid modifications is an amino acid insertion.
7. The modified IgG according to claim 1, 2 or 3 which has a higher affinity for FcRn than the IgG having the wild-type IgG constant domain.

8. The modified IgG according to claim 7 which has a higher affinity for the FcRn at pH 6.0 than at pH 7.4.

5 9. The modified IgG according to claim 1, wherein said one or more amino acid modifications are amino acid substitutions at one or more of positions 251, 255, 308, 309, 311, 312, 314, 385, 386, 387, 389, 428, 433, 434, or 436.

10 10. The modified IgG according to claim 2 or 3, wherein said one or more amino acid modifications are amino acid substitutions at one or more of positions 251, 252, 254, 255, 256, 308, 309, 311, 312, 314, 385, 386, 387, 389, 428, 433, 434 or 336.

15 11. The modified IgG according to claim 1 or 3 wherein said one or more amino acid modifications are substitution with leucine at position 251, substitution with tyrosine, tryptophan or phenylalanine at position 252, substitution with threonine or serine at position 254, substitution with arginine at position 255, substitution with glutamine, arginine, serine, threonine, or glutamate at position 256, substitution with threonine at position 308, substitution with proline at position 309, substitution with serine at position 311, substitution with aspartate at position 312, substitution with leucine at position 314, substitution with
20 arginine, aspartate or serine at position 385, substitution with threonine or proline at position 386, substitution with arginine or proline at position 387, substitution with proline, asparagine or serine at position 389, substitution with methionine or threonine at position 428, substitution with tyrosine or phenylalanine at position 434, substitution with histidine, arginine, lysine or serine at position 433, or substitution with histidine, tyrosine, arginine or
25 threonine at position 436.

12. The modified IgG according to claim 11, wherein said one or more amino acid substitutions are substitutions with tyrosine at position 252, threonine at position 254 and glutamate at 256.

30 13. The modified IgG according to claim 11, wherein said one or more amino acid substitutions are substitutions with lysine at position 433, phenylalanine at position 434 and histidine at position 436.

35 14. The modified IgG according to claim 11, wherein said amino acid substitution is a substitution with tyrosine or tryptophan at position 252.

15. The modified IgG according to claim 2 wherein said one or more amino acid modifications are substitution with leucine at position 251, substitution with tyrosine, tryptophan or phenylalanine at position 252, substitution with threonine at position 254, substitution with arginine at position 255, substitution with glutamine, arginine, serine, threonine, or glutamate at position 256, substitution with threonine at position 308, substitution with proline at position 309, substitution with serine at position 311, substitution with aspartate at position 312, substitution with leucine at position 314, substitution with arginine, aspartate or serine at position 385, substitution with threonine or proline at position 386, substitution with arginine or proline at position 387, substitution with proline, asparagine or serine at position 389, substitution with methionine or threonine at position 428, substitution with tyrosine or phenylalanine at position 434, substitution with histidine, arginine, lysine or serine at position 433, or substitution with histidine, tyrosine, arginine or threonine at position 436.

16. The modified IgG according to claim 15, wherein said one or more amino acid substitutions are substitution with tyrosine at position 252, threonine at position 254 and glutamate at 256.

17. The modified IgG according to claim 15, wherein said one or more amino acid substitutions are substitution with lysine at position 433, phenylalanine at position 434 and histidine at position 436.

18. The modified IgG according to claim 15, wherein said amino acid substitution is a substitution with tyrosine or tryptophan at position 252.

19. The modified IgG according to claim 3 or 15 which has the heavy chain variable domain and light chain variable domain of SYNAGIS®.

20. The modified IgG according to claim 3 or 15 which has the heavy chain variable domain and light chain variable domain of AFFF, p12f2, p12f4, p11d4, A1e109, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L215B10, A13A11, A1H5, A4B4(1), A4B4L1FR-S28R, or A4B4-F52S.

21. A fusion protein comprising a non-IgG polypeptide covalently linked to a modified IgG constant domain, or a fragment thereof that binds to FcRn, said modified IgG

constant domain or fragment comprising one or more amino acid modifications relative to a wild-type IgG constant domain, wherein the one or more modifications are at one or more of positions 251, 253, 255, 285-290, 308-314, 385-389, and 428-436, and wherein said fusion protein has a longer half life than the non-IgG polypeptide alone.

22. A fusion protein comprising a non-IgG polypeptide covalently linked to a modified non-human IgG constant domain, or a fragment thereof that binds to FcRn, said modified non-human IgG constant domain or fragment comprising one or more amino acid modifications relative to a wild-type non-human IgG constant domain, wherein the one or more modifications are at one or more of positions 251-256, 285-290, 308-314, 385-389, and 428-436, with the proviso that the modified amino acid sequence does not have leucine at position 252, serine at position 254, and phenylalanine at position 256, and wherein said fusion protein has a longer half life than the non-IgG polypeptide alone.

23. A fusion protein comprising a non-IgG polypeptide covalently linked to a modified human IgG constant domain, or a fragment thereof that binds to FcRn, said modified human IgG constant domain or fragment comprising one or more amino acid modifications relative to a wild-type human IgG constant domain, wherein the one or more modifications are at one or more of positions 251-256, 285-290, 308-314, 385-389, and 428-436, and wherein said fusion protein has a longer half life than the non-IgG polypeptide alone.

24. The fusion protein according to claim 21, 22, or 23, wherein at least one of the amino acid modifications is an amino acid substitution.

25. The fusion protein according to claim 21, 22, or 23, wherein at least one of the amino acid modifications is an amino acid deletion.

26. The fusion protein according to claim 21, 22, or 23, wherein at least one of the amino acid modifications is an amino acid insertion.

27. The fusion protein according to claim 21, 22, or 23, wherein the modified IgG constant domain or fragment has an increased affinity for FcRn relative to the wild-type IgG constant domain.

28. The fusion protein according to claim 27, wherein the modified IgG constant domain or fragment has a higher affinity for the FcRn at pH 6.0 than at pH 7.4.

5 29. The fusion protein according to claim 21, 22, or 23, wherein the non-IgG polypeptide is an immunoglobulin.

30. The fusion protein according to claim 21, wherein the one or more amino acid modifications are amino acid substitutions at one or more of positions 251, 255, 308, 309,
10 311, 312, 314, 385, 386, 387, 389, 428, 433, 434, or 436.

31. The fusion protein according to claim 22 or 23, wherein the one or more amino acid modifications are amino acid substitutions at one or more of positions 251, 252, 254, 255, 256, 308, 309, 311, 312, 314, 385, 386, 387, 389, 428, 433, 434 or 336.

15 32. The fusion protein according to claim 21 or 23, wherein said one or more amino acid modifications are substitution with leucine at position 251, substitution with tyrosine, tryptophan or phenylalanine at position 252, substitution with threonine or serine at position 254, substitution with arginine at position 255, substitution with glutamine, arginine,
20 serine, threonine, or glutamate at position 256, substitution with threonine at position 308, substitution with proline at position 309, substitution with serine at position 311, substitution with aspartate at position 312, substitution with leucine at position 314, substitution with arginine, aspartate or serine at position 385, substitution with threonine or proline at position 386, substitution with arginine or proline at position 387, substitution with proline,
25 asparagine or serine at position 389, substitution with methionine or threonine at position 428, substitution with tyrosine or phenylalanine at position 434, substitution with histidine, arginine, lysine or serine at position 433, or substitution with histidine, tyrosine, arginine or threonine at position 436.

30 33. The fusion protein according to claim 32, wherein said one or more amino acid substitutions are substitutions with tyrosine at position 252, threonine at position 254 and glutamate at 256.

34. The fusion protein according to claim 32, wherein said one or more amino
35 acid substitutions are substitutions with lysine at position 433, phenylalanine at position 434 and histidine at position 436.

35. The fusion protein according to claim 32, wherein said amino acid substitution is a substitution with tyrosine or tryptophan at position 252.

5 36. The fusion protein according to claim 32, wherein said one or more amino acid modifications are substitution with leucine at position 251, substitution with tyrosine, tryptophan or phenylalanine at position 252, substitution with threonine at position 254, substitution with arginine at position 255, substitution with glutamine, arginine, serine, threonine, or glutamate at position 256, substitution with threonine at position 308,
10 substitution with proline at position 309, substitution with serine at position 311, substitution with aspartate at position 312, substitution with leucine at position 314, substitution with arginine, aspartate or serine at position 385, substitution with threonine or proline at position 386, substitution with arginine or proline at position 387, substitution with proline, asparagine or serine at position 389, substitution with methionine or threonine at position
15 428, substitution with tyrosine or phenylalanine at position 434, substitution with histidine, arginine, lysine or serine at position 433, or substitution with histidine, tyrosine, arginine or threonine at position 436.

20 37. The fusion protein according to claim 36, wherein said one or more amino acid substitutions are substitutions with tyrosine at position 252, threonine at position 254 and glutamate at 256.

25 38. The fusion protein according to claim 36, wherein said one or more amino acid substitutions are substitutions with lysine at position 433, phenylalanine at position 434 and histidine at position 436.

39. The fusion protein according to claim 36, wherein said amino acid substitution is a substitution with tyrosine or tryptophan at position 252.

30 40. A molecule comprising a non-protein agent conjugated to a modified IgG constant domain, or a fragment thereof that binds to FcRn, said modified IgG constant domain or fragment comprising one or more amino acid modifications relative to a wild-type IgG constant domain, wherein the one or more modifications are at one or more of positions 251, 253, 255, 285-290, 308-314, 385-389, and 428-436, and wherein said molecule has a
35 longer half life than the non-protein agent alone.

41. A molecule comprising a non-protein agent conjugated to a modified non-human IgG constant domain, or a fragment thereof that binds to FcRn, said modified non-human IgG constant domain or fragment comprising one or more amino acid modifications relative to a wild-type non-human IgG constant domain, wherein the one or more
5 modifications are at one or more of positions 251-256, 285-290, 308-314, 385-389, and 428-436, with the proviso that the modified amino acid sequence does not have leucine at position 252, serine at position 254, and phenylalanine at position 256, and wherein said molecule has a longer half life than the non-protein agent alone.

10 42. A molecule comprising a non-protein agent conjugated to a modified human IgG constant domain, or a fragment thereof that binds to FcRn, said modified human IgG constant domain or fragment comprising one or more amino acid modifications relative to a wild-type human IgG constant domain, wherein the one or more modifications are at one or
15 more of positions 251-256, 285-290, 308-314, 385-389, and 428-436, and wherein said molecule has a longer half life than the non-protein agent alone.

43. The molecule according to claim 40, 41, or 42 wherein at least one of the amino acid modifications is an amino acid substitution.

20 44. The molecule according to claim 40, 41, or 42 wherein at least one of the amino acid modifications is an amino acid deletion.

25 45. The molecule according to claim 40, 41 or 42, wherein at least one of the amino acid modifications is an amino acid insertion.

46. The molecule according to claim 40, 41 or 42, wherein the modified IgG constant domain or fragment has an increased affinity for FcRn relative to the wild-type constant domain.

30 47. The molecule according to claim 46, wherein the modified IgG constant domain or fragment has a higher affinity for the FcRn at pH 6.0 than at pH 7.4.

35 48. The molecule according to claim 40, wherein the one or more amino acid modifications are amino acid substitutions at one or more of positions 251, 255, 308, 309, 311, 312, 314, 385, 386, 387, 389, 428, 433, 434, or 436.

49. The molecule according to claim 41 or 42, wherein the one or more amino acid modifications are substitution at one or more of positions 251, 252, 254, 255, 256, 308, 309, 311, 312, 314, 385, 386, 387, 389, 428, 433, 434 or 336.

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50. The molecule according to claim 40 or 42, wherein said one or more amino acid modifications are substitution with leucine at position 251, substitution with tyrosine, tryptophan or phenylalanine at position 252, substitution with threonine or serine at position 254, substitution with arginine at position 255, substitution with glutamine, arginine, serine, threonine, or glutamate at position 256, substitution with threonine at position 308, substitution with proline at position 309, substitution with serine at position 311, substitution with aspartate at position 312, substitution with leucine at position 314, substitution with arginine, aspartate or serine at position 385, substitution with threonine or proline at position 386, substitution with arginine or proline at position 387, substitution with proline, asparagine or serine at position 389, substitution with methionine or threonine at position 428, substitution with tyrosine or phenylalanine at position 434, substitution with histidine, arginine, lysine or serine at position 433, or substitution with histidine, tyrosine, arginine or threonine at position 436.

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51. The molecule according to claim 50, wherein said one or more amino acid substitutions are substitutions with tyrosine at position 252, threonine at position 254 and glutamate at 256.

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52. The molecule according to claim 50, wherein said one or more amino acid substitutions are substitutions with lysine at position 433, phenylalanine at position 434 and histidine at position 436.

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53. The molecule according to claim 50, wherein said amino acid substitution is a substitution with tyrosine or tryptophan at position 252.

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54. The molecule according to claim 41, wherein said one or more amino acid modifications are substitution with leucine at position 251, substitution with tyrosine, tryptophan or phenylalanine at position 252, substitution with threonine at position 254, substitution with arginine at position 255, substitution with glutamine, arginine, serine, threonine, or glutamate at position 256, substitution with threonine at position 308, substitution with proline at position 309, substitution with serine at position 311, substitution

with aspartate at position 312, substitution with leucine at position 314, substitution with arginine, aspartate or serine at position 385, substitution with threonine or proline at position 386, substitution with arginine or proline at position 387, substitution with proline, asparagine or serine at position 389, substitution with methionine or threonine at position 428, substitution with tyrosine or phenylalanine at position 434, substitution with histidine, arginine, lysine or serine at position 433, or substitution with histidine, tyrosine, arginine or threonine at position 436.

55. The molecule according to claim 54, wherein said one or more amino acid substitutions are substitutions with tyrosine at position 252, threonine at position 254 and glutamate at 256.

56. The molecule according to claim 54, wherein said one or more amino acid substitutions are substitutions with lysine at position 433, phenylalanine at position 434 and histidine at position 436.

57. The molecule according to claim 54, wherein said amino acid substitution is a substitution with tyrosine or tryptophan at position 252.

58. A pharmaceutical composition comprising the modified human or humanized IgG according to claim 3 and a pharmaceutically acceptable carrier.

59. A pharmaceutical composition comprising the fusion protein according to claim 23 and a pharmaceutically acceptable carrier.

60. A pharmaceutical composition comprising the molecule according to claim 42 and a pharmaceutically acceptable carrier.

61. A method of treating a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of the modified human or humanized IgG according to claim 3.

62. The method according to claim 61 which comprises passive immunotherapy.

63. A method of treating a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of the fusion protein according to claim 23.

5 64. A method of treating a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of the molecule according to claim 42.

10 65. A nucleic acid comprising a nucleotide sequence encoding the modified IgG constant domain according to claim 1, 2 or 3, or an FcRn binding fragment thereof.

66. A nucleic acid comprising a nucleotide sequence encoding the fusion protein according to claim 21, 22, or 23.

15 67. A host cell comprising the nucleic acid according to claim 65.

68. A host cell comprising the nucleic acid according to claim 66.

20 69. A kit comprising the modified human or humanized IgG according to claim 3.

70. A kit comprising the fusion protein according to claim 23.

71. A kit comprising the molecule according to claim 42.

25 72. A method of preventing a disease or disorder comprising administering to a subject a prophylactically effective amount of the modified human or humanized IgG according to claim 3.

30 73. The method according to claim 72 which is passive immunotherapy.

74. The method according to claim 72 wherein the disease is RSV infection.

35 75. The method according to claim 74, wherein said modified human or humanized IgG is a modified SYNAGIS® antibody.

76. The method according to claim 74, wherein said modified human or humanized IgG is a modified AFFF, p12f2, p12f4, p11d4, Ale109, A12a6, A13c4, A17d4, A4B4, A8C7, 1X-493L1FR, H3-3F4, M3H9, Y10H6, DG, AFFF(1), 6H8, L1-7E5, L215B10, A13A11, A1H5, A4B4(1), A4B4L1FR-S28R or A4B4-F52S antibody.

77. A method of vaccinating a subject comprising administering to said subject an amount of the modified human or humanized IgG according to claim 3 effective to elicit an immune response.

78. A method of vaccinating a subject comprising administering to said subject an amount of the fusion protein according to claim 23 effective to elicit an immune response.

79. The method according to 61 which comprises administering a dose of said modified human or humanized IgG that is lower than the lowest therapeutically effective dose of a second IgG identical to said modified human or humanized IgG except that said second IgG lacks said one or more amino acid modifications.

80. The method according to claim 79 which results in fewer or less severe side effects than administration of the therapeutically effective dose of the second IgG.

81. The method according to claim 61 which comprises administering a therapeutically effective dosing schedule having less frequent doses of said modified human or humanized IgG than the therapeutically effective dosing schedule having the least frequent dosing of a second IgG identical to said modified human or humanized IgG except that said second IgG lacks said one or more amino acid modifications.

82. The method according to claim 72 which comprises administering a prophylactically effective dose of said modified human or humanized IgG that is lower than the lowest prophylactically effective dose of a second IgG identical to said modified human or humanized IgG except that said second IgG lacks said one or more amino acid modifications.

83. The method according to claim 82 which results in fewer or less severe side effects than administration of the prophylactically effective dose of the second IgG.

84. The method according to claim 72 which comprises administering a prophylactically effective dosing schedule having less frequent doses of said modified human or humanized IgG than the prophylactically effective dosing schedule with the least frequent dosing of a second IgG identical to said human or humanized IgG except that said second IgG lacks said one or more amino acid modifications.

85. A method of *in vivo* diagnosis in a subject comprising:

- (a) administering to a subject an effective amount of the modified human or humanized IgG according to claim 3 labeled with a detectable marker, said modified human or humanized IgG specifically binding to an antigen associated with a disease or disorder;
- (b) allowing the modified human or humanized IgG to concentrate at sites in said subject where said antigen is found; and
- (c) detecting said detectable marker,

whereby detection of said detectable marker above a background or standard level indicates that the subject has said disease or disorder.

86. The modified human or humanized IgG according to claim 3 which immunospecifically binds to an RSV antigen.